Vardenafil in the Treatment of Erectile Dysfunction in Outpatients With Chronic Schizophrenia: A Flexible-Dose, Open-Label Study

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This study was not supported by external funding.

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Objective: The aim of this study was to evaluate the safety and efficacy of vardenafil in outpatients with chronic schizophrenia and erectile dysfunction and to investigate any effect on quality of life in this population.

Method: In this 12-week, open-label, flexible-dose study, 25 outpatients with chronic schizophrenia (DSM-IV criteria) and erectile dysfunction received vardenafil 10 mg as needed (at a maximum of 1 dose per day) with the option to maintain current dose or to titrate to 5 mg or 20 mg at 4 and 8 weeks. Assessment was performed with the International Index of Erectile Function (IIEF) at base line and at weeks 4, 8, and 12. The Quality of Life Scale (QLS) was administered at baseline and at week 12. The study was carried out at the Psychiatric Hospital of Athens, Greece, between October 2005 and November 2006.

Results: Vardenafil produced a statistically significant improvement in all IIEF domains [erectile function ($p < .001$), orgasmic function ($p < .05$), sexual desire ($p < .05$), intercourse satisfaction ($p < .01$), and overall satisfaction ($p < .001$)] and QLS ($p < .003$). Results were similar for the intention-to-treat (N = 25) and completer (N = 21, 84%) groups. Adverse events were infrequent and decreased in incidence over the course of the study.

Conclusion: Vardenafil was generally well tolerated and highly effective in outpatients with chronic schizophrenia and erectile dysfunction. The response to vardenafil was not influenced by certain patient characteristics, such as erectile dysfunction severity or serum prolactin levels. Improvement in sexual function was correlated with improvement in the quality of life.

(J Clin Psychiatry 2008;69:206–212)

Erectile dysfunction (ED) is one of the most common male sexual disorders, affecting more than 150 million men worldwide.[1,2] Erectile dysfunction is also a significant problem faced by people with schizophrenia.[3] The prevalence of sexual dysfunction in patients with schizophrenia has been underreported, primarily due to the hesitation of patients and psychiatrists to discuss this issue.[4] Impaired sexual functioning is believed to negatively impact treatment compliance and disease prognosis, as well as the quality of life of these patients.[5,6] Both the illness and antipsychotic medication have been implicated.[3] Erectile dysfunction may contribute to, or be a consequence of, schizophrenic symptoms.[7] Several variables can be involved, including psychotic symptoms and depression, as well as loss of self esteem, performance anxiety, and impairment of quality of life. On the other hand, most classes of antipsychotic drugs are implicated in sexual dysfunction.[8–10] Antipsychotics may induce ED by multiple mechanisms, including direct dopamine type 2 (D_2) blockade, prolactin elevation, sedation, extrapyramidal side effects, and antagonism, at cholinergic and α-adrenergic receptors. Furthermore, there is growing evidence to suggest that second-generation antipsychotics are associated with increased risk of metabolic syndrome.[11] Metabolic syndrome may contribute to a higher incidence of sexual dysfunction (high blood pressure, obesity, risk of developing diabetes, and/or cardiovascular disease).[9]

Treatment for ED in patients with schizophrenia should be reliably effective, simple to use, and have

minimal side effects. Treatment options, such as discontinuation of the antipsychotic medication, addition of a dopamine agonist (e.g., bromocriptine, amantadine),[12] or other strategies, such as injections into the corpora cavernosa, vacuum devices, or transurethral delivery of drugs to enhance erectile function, that may be unacceptable or painful to the patient[2] are associated with high rates of discontinuation or dissatisfaction and can increase the risk for a relapse of the psychotic symptomatology.[8,9] Treatment for ED has been revolutionized by the availability of the phosphodiesterase-5 (PDE-5) inhibitors, which are both effective and well tolerated.[13] PDE-5 inhibitors competitively inhibit cyclic guanosine monophosphate breakdown, and thus promote smooth muscle relaxation, vascular engorgement, and penile erection. Nitric oxide is considered as the principal neurotransmitter mediating penile erection and activates guanylate cyclase, which converts guanosine triphosphate into cyclic guanosine monophosphate, ultimately reducing intracellular calcium levels to bring about smooth muscle relaxation. PDE-5 predominates in penile tissue and functions to hydrolyze cyclic guanosine monophosphate, reversing the effects of nitric oxide and preventing sustained erection. PDE-5 inhibitors enhance erectile function by maintaining sufficient accumulation of cyclic guanosine monophosphate in the corpus cavernosum and contributing blood vessels.[14]

Positive anecdotal reports about sildenafil regarding the role of PDE-5 inhibitors in schizophrenic patients with ED have been published,[15–18] and only 1 double-blind, placebo-controlled study.[19] To our knowledge, none of the studies reported to date have investigated the potential beneficial effect that PDE-5 inhibitor therapy may have on mental health and quality of life in patients with chronic schizophrenia and ED.

Vardenafil is a potent and selective oral PDE-5 inhibitor that has been shown to be effective and reliable and a generally well-tolerated treatment in a broad population of men with ED (organic, psychogenic, or mixed).[20,21] It has been reported to be 10 times more potent as a PDE-5 inhibitor than sildenafil and more selective for PDE-5 over PDE-6 and PDE-11.[22]

The aim of this flexible-dose, open-label, 12-week study was to assess the safety and efficacy of vardenafil in outpatients with chronic schizophrenia and ED and to investigate any effect on quality of life in this population.

METHOD

Study Participants

Subjects were outpatients, 18 years of age or older, who met criteria for schizophrenia according to the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition (DSM-IV).[23] Diagnosis of schizophrenia was required to have been made at least 2 years prior to entry, and continued antipsychotic treatment during this period was required in order to classify the diagnosis as chronic. All male patients with chronic schizophrenia who underwent a monthly follow-up in the outpatients' clinic of the Psychiatric Hospital of Athens were invited to participate in the study. Only those patients who reported having ED for at least 6 months prior to study initiation were included. Erectile dysfunction was defined as a persistent or recurrent inability to attain, or to maintain until completion of the sexual activity, an adequate erection. The disturbance caused marked distress or interpersonal difficulty (DSM-IV criteria). Participants had to be married or participating in a stable heterosexual relationship for more than 6 months. Each patient's condition at entry had to be stable (no significant improvement or worsening of symptoms within the past 3 months). Baseline stability was assessed with the use of the Positive and Negative Syndrome Scale (PANSS).[24] Significant improvement (or worsening) was defined as a greater than 20% reduction (or increase, respectively) in the PANSS total score or in the PANSS positive or negative symptom subscale scores. Patients were required to have remained on a stable dose of their antipsychotic regimen for at least 6 months prior to study initiation.

All patients had to be physically healthy. A detailed history was elicited, and a physical examination and laboratory tests were performed to exclude medical causes of ED: arterial hypertension, peripheral vascular disease, atherosclerosis, history of myocardial infarction or stroke, diabetes mellitus, thyroid disease, clinically significant renal or hepatic insufficiency, cancer and cancer treatment, multiple sclerosis, penile anatomical abnormalities, surgical procedures associated with ED (e.g., spinal and abdominal surgery), retinitis pigmentosa, or history of radical prostatectomy. Patients were also excluded if they had a psychiatric disorder other than schizophrenia, met criteria for substance dependence or mental retardation, presented suicidal ideation, or were considered to be at significant suicide risk by the investigator. Other exclusion criteria were a history of seizures, hypersensitivity to vardenafil or other PDE-5 inhibitors, or regular use of nitrates, anticoagulants, or aspirin. The use of other measures to improve erectile function was also prohibited during the study. Patients were excluded from the study if they were experiencing acute relapse. Acute relapse was defined as an impending decompensation based on a PANSS score of 4 or higher (moderate) on the subscale items of hostility and uncooperativeness and/or a 20% or greater increase in the PANSS total score.

Study Design

The study was conducted in the Psychiatric Hospital of Athens, Greece, the largest state psychiatric institution in the country, between October 2005 and November

2006, in accordance with the protocol and ethical principles stated in the Declaration of Helsinki, and was approved by the institutional review board of the Psychiatric Hospital of Athens. Written informed consent was obtained from all participants after a complete description of the study had been given to them.

After a 4-week run-in period during which no medication or device for ED was permitted, the patients were assigned to receive vardenafil. The starting dose of vardenafil in the first 4 weeks was 10 mg. Patients were instructed to take 1 dose of vardenafil with or without food about 1 hour before sexual intercourse, with a maximum of 1 dose per calendar day. At week 4, the investigator and each patient, on the basis of the efficacy and tolerability of the initial dose, decided whether the initial dose should be maintained, increased to 20 mg/day, or decreased to 5 mg/day for the next 4 weeks. At week 8, the patients had the choice to continue taking their current dose or to change by 1 dose level to 5 mg/day, 10 mg/day, or 20 mg/day for use until the end of the study, also in consultation with the investigator.

Assessment

Sexual function. The International Index of Erectile Function (IIEF) was used for the evaluation of sexual function.[25] Severity of ED was graded according to baseline IIEF-erectile function domain scores: none (26–30), mild (17–25), moderate (11–16), and severe (< 11).[26] Sexual function was assessed at baseline (end of run-in period) and at weeks 4, 8, and 12. Efficacy was evaluated on the basis of IIEF-erectile function scores, in which a clinically significant improvement was defined as an increase of 5 points or more. Return to normal erectile function was defined as an erectile function domain score of 26 or higher.

The IIEF is a validated, multidimensional, self-administered questionnaire that provides accurate and reliable information as a quantitative index of ED severity. It is widely employed to assess therapeutic efficacy of ED therapy. It comprises 15 questions arranged into 5 domains: erectile function (questions 1–5 and 15; possible score 1–30), orgasmic function (questions 9 and 10; possible score 1–10), sexual desire (questions 11 and 12; possible score 2–10), intercourse satisfaction (questions 6–8; possible score 0–15), and overall satisfaction (questions 13 and 14; possible score 2–10).

Quality of life. The Quality of Life Scale (QLS)[27] was administered at baseline and at week 12. The QLS is a 21-item clinician rating scale that was developed to assess symptoms in the course and treatment of schizophrenia. It involves a semistructured interview and ratings based on the patient's self report and the clinician's professional judgment of the patient's functioning and life circumstances. Each item is rated on a 7-point scale from 0 or 1 (severe impairment of function) to 5 or 6 (normal or unimpaired). The measure is scored into the following 4 categories: intrapsychic foundations (7 items), interpersonal relations (8 items), instrumental role (4 items), and common objects and activities (2 items). There is also an overall score.

Safety assessment. A full physical examination and blood laboratory tests, including hematology and serum chemistries, were performed at screening and at the end of the study, or at early discontinuation. A 12-lead electrocardiogram was also performed at the first visit. Measurements of heart rate and blood pressure were obtained at each visit. Moreover, serum prolactin levels were assessed at study initiation. All observed and spontaneously reported adverse events related to vardenafil were recorded at each study visit. All patients who had received at least 1 dose of vardenafil were included in the safety assessment.

Statistical Analysis

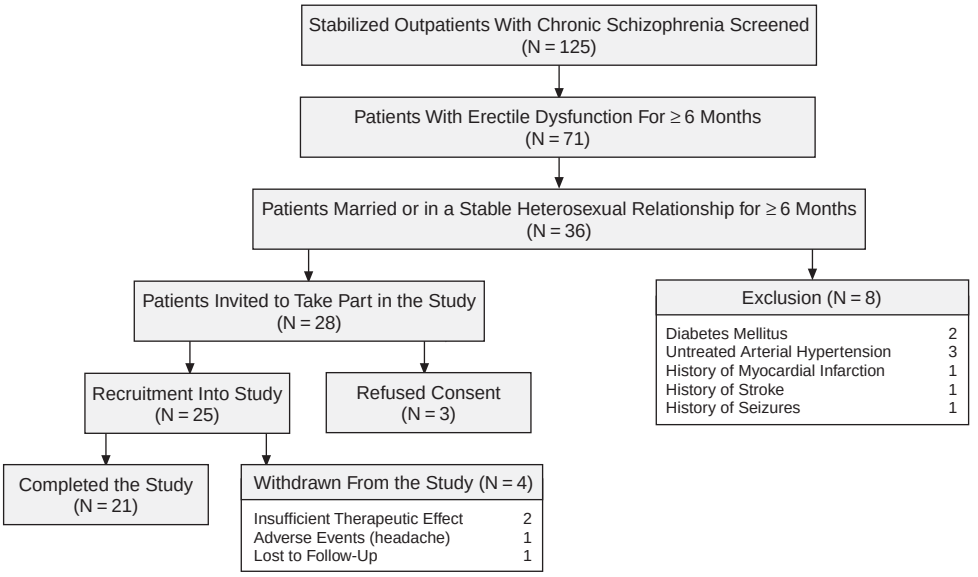
Repeated-measures analysis of variance was used to test the change of clinical data over time (at baseline and at 4, 8, and 12 weeks). Data were analyzed for the intention-to-treat group, and the analyses were repeated for the subgroup meeting the criteria for study completion. The intention-to-treat group included patients who took at least 1 dose of vardenafil and who had baseline and any postbaseline efficacy data. Analysis of the 5 domains of the IIEF score and the QLS score was based on the intention-to-treat group by using the last-observation-carried-forward method to account for dropouts. A subgroup analysis was conducted to evaluate significant interactions between groups, according to baseline ED severity. Additional subgroup analyses were performed for patients with raised serum prolactin levels. Pearson correlations were used as measures of association between changes in IIEF domains and QLS from baseline to week 12. Statistical significance was set as $p < .05$. All statistical analyses were performed using the Statistical Package for Social Sciences for Windows (SPSS 14.0 for Windows, SPSS Inc., Chicago, Ill.).

RESULTS

Patient Disposition

The follow-up details are given in Figure 1. The 25 patients recruited for the study, after a 4-week run-in period, were assigned to receive 10 mg of vardenafil "as needed" (maximum 1 dose per day) for 4 weeks. At week 4, 17 patients, in collaboration with the investigator, chose to increase the dosage to 20 mg, and 1 patient chose to decrease the dosage from 10 to 5 mg. At week 8, 2 more patients switched to a 20 mg dose. The majority of the patients taking vardenafil (N = 19, 76%) opted to titrate to the 20 mg dose by the end of treatment. Eighty-four percent (21/25) of the participants completed the

Figure 1. Flow Diagram of the Study of Vardenafil in the Treatment of Erectile Dysfunction in Outpatients With Chronic Schizophrenia



study. Premature discontinuation was attributed to adverse events (N = 1, 4%), insufficient therapeutic effect (N = 2, 8%), or loss to follow-up (N = 1, 4%). These 4 patients withdrew from the study after the week 4 assessment, resulting in 25 patients being included in the intention-to-treat analysis. Of the 25 patients in the intention-to-treat group at baseline, 5 (20%) presented with mild ED, 14 (56%) with moderate ED, and 6 (24%) with severe ED.

Patient Demographics and Clinical Characteristics

The mean age of participants was 47.0 (SD = 12.4) years, their mean educational level was 9.2 (SD = 3.5) years, and their mean number of lifetime psychiatric hospitalizations was 2.6 (SD = 1.5) with the first occurring at a mean age of 31.9 (SD = 10.0) years. First manifestation of the disease was at a mean age of 25.3 (SD = 8.3) years. The mean serum prolactin levels were 20.9 ng/mL (SD = 17.4) (prolactin normal range: 2.5–17 ng/mL). The patients were taking a mean dose of 510.0 (SD = 331.6) mg of chlorpromazine equivalents.

The DSM-IV schizophrenia subtypes were as follows: paranoid type (N = 17, 68%), undifferentiated type (N = 2, 8%), and residual type (N = 6, 24%). They were taking the following antipsychotic medications: clozapine (N = 8, 32%), risperidone (N = 7, 28%), amisulpride (N = 4, 16%), olanzapine (N = 3, 12%), haloperidol (N = 2, 8%), and aripiprazole (N = 1, 4%). Five patients were taking biperiden in a mean dose of 3.2 mg/day (SD = 0.4). Four patients were also taking diazepam in a mean dose of 5.6 mg/day (SD = 1.5).

Efficacy

The demographic and clinical characteristics did not differ significantly between trial completers (N = 21) and noncompleters (N = 4). Due to the small sample size of the noncompleter group, low-power comparative analysis was not undertaken.

A statistically significant improvement in IIEF-erectile function domain scores was seen at the last observation carried forward (Table 1). The results were similar for those who completed the treatment period (N = 21). An increase of at least 5 points in the IIEF-erectile function score relative to baseline was observed in 76% (16/21) of the patients who completed the study. A return to a normal erectile function domain score (≥ 26) was reported by 40% (10/25) of the patients at the end of the study. All other IIEF domain scores, evaluating intercourse satisfaction, overall satisfaction, orgasmic function, and sexual desire, showed statistically significant improvement (Table 1). Results were similar for the intention-to-treat and completer groups. There was a statistically significant improvement in the total score of the QLS and in 3 of the 4 subscales (intrapsychic foundations, interpersonal relations, and common objects and activities) at the end of the study. As the subgroup analysis showed, IIEF domains and QLS scores were not influenced by the baseline ED severity, since there were no time-by-group significant interactions ($p > .05$).

Associations between individual changes in the scores of the IIEF-erectile function domain and the QLS were tested with the use of Pearson correlations. A positive correlation was observed between individual changes in

Table 1. Clinical Ratings (mean score ± SD) Over the Course of the 12-Week Study of Vardenafil in the Treatment of Erectile Dysfunction in Outpatients With Chronic Schizophrenia

					Analysis[a,b]		
Instrument	Baseline	Week 4	Week 8	Week 12	df	F	p Value
IIEF-erectile function	13.0 ± 3.4	14.6 ± 3.9	18.4 ± 5.6	20.7 ± 6.6	3,57	28.3	< .001
IIEF-orgasmic function	5.1 ± 1.2	5.2 ± 1.4	5.4 ± 2.1	6.0 ± 1.2	3,57	3.7	< .05
IIEF-sexual desire	5.8 ± 1.2	5.9 ± 1.3	6.2 ± 1.6	6.6 ± 1.9	3,57	3.8	< .05
IIEF-intercourse satisfaction	6.5 ± 1.4	6.8 ± 1.9	7.6 ± 2.0	7.7 ± 2.4	3,57	4.7	< .01
IIEF-overall satisfaction	5.1 ± 1.1	5.5 ± 1.5	6.3 ± 1.6	6.7 ± 1.9	3,57	17.5	< .001
QLS Total	56.7 ± 8.6	…	…	61.4 ± 11.3	1,19	13.9	< .003
Intrapsychic foundations	20.3 ± 3.4	…	…	22.5 ± 4.7	1,19	18.2	< .001
Interpersonal relations	18.9 ± 2.7	…	…	21.0 ± 4.4	1,19	12.4	< .002
Instrumental role	10.8 ± 3.7	…	…	10.9 ± 4.1	1,19	1.8	NS
Common objects and activities	6.6 ± 1.8	…	…	7.0 ± 1.9	1,19	7.0	< .05

[a]Data were analyzed according to the intention to treat (N = 25), with the last observation carried forward.
[b]Repeated-measures analysis of variance.
Abbreviations: IIEF = International Index of Erectile Function, NS = not significant, QLS = Quality of Life Scale.
Symbol: … = not applicable.

IIEF-erectile function domain and QLS [N = 25, r = 0.45, p = .02].

Safety and Tolerability

Vardenafil was generally well tolerated. The most frequently reported treatment-emergent adverse events included headache, flushing, nasal congestion, dyspepsia, and orthostatic hypotension (Table 2). These adverse events are generally reported with all PDE-5 inhibitors. Adverse events decreased in incidence over the course of the study. No other adverse events or clinically significant findings related to vital signs and laboratory analyses were reported. One patient (4%) discontinued due to adverse events that were considered by the investigator as possibly related to vardenafil. This was a 40-year-old patient who had been maintained on aripiprazole therapy at a dose of 30 mg/day for the last 12 months. After using vardenafil 10 mg, he reported persistent headache that lasted for 2 to 3 hours and did not respond to common analgesics. After the first 4 weeks of the study, the patient and the investigator decided to decrease the dose to 5 mg, without any improvement in the headache. The patient discontinued after week 8 of the study.

Table 2. Treatment-Emergent Adverse Events During a 12-Week Study of Vardenafil in the Treatment of Erectile Dysfunction in Outpatients With Chronic Schizophrenia

	Week 4 (N = 25)		Week 8 (N = 24)		Week 12 (N = 21)	
Adverse Event	N	%	N	%	N	%
Headache	3	12.0	2	8.3	1	4.8
Flushing	2	8.0	1	4.2	0	0.0
Nasal congestion	1	4.0	0	0.0	0	0.0
Dyspepsia	0	0.0	1	4.2	0	0.0
Orthostatic hypotension	1	4.0	0	0.0	0	0.0

Patients With Raised Serum Prolactin Levels

The standardized normal range of serum prolactin in our laboratory is 2.5 to 17 ng/mL. Twelve patients (48%) showed raised serum prolactin levels at baseline. No significant interactions between IIEF domains, QLS, and serum prolactin levels could be detected (p > .05). The results show that vardenafil is also effective in the subgroup of participants with an elevated serum prolactin level.

DISCUSSION

Erectile dysfunction is a widespread, age-related medical condition that affects more than 50% of men aged 40 to 70 years.[2] The introduction of the oral PDE-5 inhibitors markedly changed the therapeutic approach to ED, offering a safe and efficacious option in restoring the ability to achieve and sustain an erection. Erectile dysfunction is a significant problem also among people with schizophrenic disorders.[3] In a large (N = 7655), prospective, cross-cultural study, Dossenbach et al.[4] state that approximately 50% of schizophrenic patients experience sexual dysfunction. Sexual function is an important aspect of quality of life, and it is often compromised in schizophrenia.[6] To the best of our knowledge, this is the first study to examine—in a prospective way—the safety and efficacy of vardenafil in patients with chronic schizophrenia and ED, and to investigate the potential benefits of PDE-5 inhibitor therapy on quality of life in this difficult-to-treat population. In this open-label, flexible-dose study, vardenafil treatment showed significant improvement in men with chronic schizophrenia at each level of baseline ED severity. Vardenafil treatment produced a dose-dependent, clinically meaningful, and statistically significant improvement in all the IIEF domains. This finding is consistent with previous clinical studies, in which vardenafil improved erections of men with ED of broad etiology.[20,28] Although patients receiving vardenafil 10 mg (maximum 1 dose per day) for the first 4 weeks present a mild positive response to this dose, as shown by the 4-week data, there was a substantial improvement of

erectile function with 20-mg doses in the final 8 weeks. This finding could be explained by the fact that 80% of the patient population was classified as having moderate or severe ED, and thus was more difficult to treat. These findings are in concordance with other studies with vardenafil, including difficult-to-treat populations.[29] The overall percentage of patients returning to a normal IIEF-erectile function domain score (≥ 26) at endpoint (40%) was comparable to that observed in diabetic[30] and prostatectomy patients.[31] The erectile function improvement, however, could bias other domains of IIEF, such as the orgasmic function domain.

There is a complex relationship between illness, treatment, and sexual functioning.[3] It remains unclear whether ED in patients with schizophrenia is due to antipsychotic treatment or is associated with the illness itself. Symptom relief is not the only measure of therapeutic success. Quality of life could be a determinant of treatment outcome. In the present study, a significant improvement has been shown in 3 of the 4 subscales of the QLS (frequency of social contacts, empathy for others, and participation in common community activities). The lack of improvement in the QLS-instrumental role subscale scores may be explained by the fact that the majority of the participants were unemployed and the duration of the study was relatively short.[32]

The high rate of ED associated with antipsychotic treatment is an important concern in terms of quality of life and treatment compliance.[5] Several studies demonstrate that sexual dysfunction is worse in patients with schizophrenia taking antipsychotic medication as compared to unmedicated patients.[7,33] In this study, vardenafil was shown to be effective in the treatment of a possibly antipsychotic-induced ED. The statistical analysis of the subgroup of patients with raised serum prolactin levels also revealed similar results. These findings are in concordance with those reported by Gopalakrishnan et al.[19] in a double-blind, placebo-controlled trial studying the efficacy and safety of the PDE-5 inhibitor sildenafil in patients with antipsychotic-induced ED. A potential explanation for these findings is that the autonomic side effects of antipsychotics may be more relevant to erection status than the degree of hyperprolactinemia.[34] It may also be that antipsychotic side effects are only a small part of a deteriorating cycle of schizophrenic illness, treatment, and ED, to which patients seem to be particularly vulnerable.

Vardenafil was generally well tolerated, with only 1 discontinuation due to adverse events. Treatment-emergent adverse events—headache, flushing, nasal congestion, dyspepsia, and orthostatic hypotension—occurred with reduced frequency over the course of the study. This safety profile is consistent with the adverse event profile of a highly selective PDE-5 inhibitor.[13] Similar low adverse event rates were reported in other clinical studies with vardenafil.[21,28] There were no adverse drug interactions observed during the study period. This fact suggests that vardenafil can be safely combined with antipsychotics.

Several study limitations merit acknowledgment:

- The sample size was relatively small.
- The sample was heterogeneous with respect to antipsychotic treatment (patients were taking various antipsychotics).
- The risk-benefit evaluation of combining vardenafil with antipsychotics may require a longer period of investigation to fully assess side effects and long-term risk.
- The potential placebo effect, the lack of a control subgroup, and the open-label study design may be considered questionable.
- The lack of objective measures of ED should be emphasized.
- Information about the sexual function during the prodromal phase and the remission periods prior to the study are not available.
- Partner's availability, relationship issues, and partner's health status were not taken into consideration in the current study.

In conclusion, this prospective, 12-week, open-label, flexible-dose study suggests that vardenafil provides an effective and generally well-tolerated treatment for ED in men with chronic schizophrenia. The response to vardenafil is not influenced by certain patient characteristics, such as ED severity or serum prolactin levels. Vardenafil may also improve other parameters associated with sexual function in patients with chronic schizophrenia, such as overall quality of life. Our preliminary findings suggest that a randomized, large-scale, double-blind, placebo-controlled trial is justified.

Drug names: amantadine (Symmetrel and others), aripiprazole (Abilify), biperiden (Akineton), bromocriptine (Parlodel and others), clozapine (Clozaril, FazaClo, and others), diazepam (Diastat, Valium, and others), haloperidol (Haldol and others), olanzapine (Zyprexa), risperidone (Risperdal), sildenafil (Revatio and Viagra), vardenafil (Levitra).

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